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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/605,498	10/02/2003	Martin Gleave	UBC.P-031	2497

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EXAMINER	
BOWMAN, AMY HUDSON	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 05/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/605,498	GLEAVE ET AL.	
	Examiner	Art Unit	
	Amy H. Bowman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *1-13,18 and 20-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-17, 19 and 25-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/12/04, 4/20/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RD

DETAILED ACTION

Applicant's election without traverse of group II, claims 14-24 and SEQ ID NO: 82, in the reply filed on 4/22/2005 is acknowledged. With the amendment filed 4/22/2005, new claims 25-28 have been added. Claims 1-28 are pending in the application. Claims 1-13, 18 and 20-24, are withdrawn as being drawn to nonelected inventions.

Notice of Non-responsive Amendment

The reply filed on 4/22/2005 is not fully responsive to the prior Office Action because of the following omission(s) or matter(s): the claims are not considered to be in compliance with 37 CFR § 1.121 due to the identifier "original, withdrawn". Appropriate correction is required.

> **§ 1.121(c) Manner of making amendments in applications.**
> (c) Claims- Amendments to a claim must be made by rewriting the entire claim with all changes (e.g., additions and deletions) as indicated in this subsection, except when the claim is being canceled. Each amendment document that includes a change to an existing claim, cancellation of an existing claim or addition of a new claim, must include a complete listing of all claims ever presented, including the text of all pending and withdrawn claims, in the application. The claim listing, including the text of the claims, in the amendment document will serve to replace all prior versions of the claims, in the application. In the claim listing, the status of every claim must be indicated after its claim number by using one of the following identifiers in a parenthetical expression: (Original), (Currently amended), (Canceled), (Withdrawn), (Previously presented), (New), and (Not entered).

Specification

The disclosure is objected to because of the following informalities: The word "antisense" is spelled "antisiense" and "anstisense" on page 3 of the specification. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14-17, 25 and 26 are rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The invention of the above claims is drawn to pharmaceutical compositions comprising a therapeutic agent, more specifically a 12 to 35 nucleotide modified antisense oligonucleotide that reduces the amount of active hsp27 in cancerous cells and a pharmaceutically acceptable carrier. The composition is packaged in a dosage unit form, wherein the dosage unit form is an injectable solution.

At the outsight, it is noted that the claims do not recite a specific target sequence by SEQ ID NO, but rather refer to the broad genus of any *hsp27* gene.

The claims encompass a pharmaceutical composition comprising any antisense to any *hsp27*, as well as encompass any *hsp27* homolog or allele from any species known or yet to be discovered of *hsp27*, as well as DNA genomic fragments, spliced variants or fragment that retains *hsp27*-like activity. Although the specification discloses oligonucleotide sequences having complementarity to a single *hsp27* sequence, the

specification does not describe oligonucleotides to any other *hsp27*, variant, homolog, or allele thereof that would describe the instantly claimed genus of any *hsp27* antisense to any *hsp27* gene. Each of the instantly disclosed oligonucleotides is targeted to a single sequence, although the claims are drawn to any antisense to any *hsp27* sequence. One of ordinary skill in the art could not make oligos to any *hsp27* without knowledge of the sequences. Since the genus embraces the breadth discussed above, and since the breadth encompassing variants, homologs, and alleles thereof could not be envisioned, applicant is not considered to be in possession of the breadth encompassing any antisense to any *hsp27* transcript.

The scope of the claimed invention is broad and the skilled artisan would not be able to envisage the entire genus claimed of antisense oligonucleotides to any *hsp27* molecule such that the skilled artisan would recognize that the applicant was in possession of the claimed genus at the time of filing. Not only do the claims broadly read on any *hsp27* in any species, but additionally the skilled artisan would not be able to envisage which antisense oligonucleotide sequences would further result in reduction of the amount of active *hsp27* in cancer cells without undue experimentation.

Thus, the instantly claimed invention cannot be said to have been adequately described in a way that would convey with reasonable clarity to those skilled in the art that, as of the filling date sought, applicant was in possession of the claimed invention because the specification does not provide a description of a sufficient number of oligonucleotides to a sufficient number of *hsp27* species that reduce the amount of active *hsp27* in cancerous cells to describe the full genus claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 14-17, 19 and 25-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Baracchini et al. (U.S. 5,801,154).

The invention of the above claims is drawn to pharmaceutical compositions comprising a therapeutic agent, more specifically a modified antisense oligonucleotide 12 to 35 nucleotides long that reduces the amount of active hsp27 in cancerous cells and a pharmaceutically acceptable carrier. The composition is packaged in a dosage unit form, wherein the dosage unit form is an injectable solution. The invention is further drawn to antisense oligonucleotide comprising a consecutive series of bases as set forth in SEQ ID NO: 82. The language "comprising a consecutive series of bases" is being interpreted as referring to comprising any consecutive series of bases in any portion of SEQ ID NO: 82.

Baracchini et al. teach antisense oligonucleotides comprising a consecutive series of bases as set forth in instant SEQ ID NO: 82. See for example, SEQ ID NO: 6, comprises a consecutive series of bases (bases 1-4, 8-10, and 12-15) as set forth in instant SEQ ID NO: 82 (bases 14-16, 18-20, and 8-11, respectively). SEQ ID NO: 6 of Baracchini et al. is 20 nucleobases in length. Additionally, Baracchini et al. teach pharmaceutical compositions comprising the antisense oligonucleotides. Baracchini et al. teach modifications to the sugar, backbone linkage and nucleobase composition (col. 6). Baracchini teaches that such modifications are desirable in antisense oligos because these modifications have desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid targets and increased stability in the presence of nucleases. Baracchini et al teach phosphorothioate linkages, 2'-O-methoxyethyl sugars, 5-methylcytosine and chimeric oligonucleotides. Baracchini et al. teach dosing, as well as injection as a method of administration (see columns 4 and 5). Although the oligonucleotides taught by Baracchini et al. are not specifically disclosed as compounds that reduce the amount of active *hsp27*, the oligonucleotides taught by Baracchini et al. meet the structural limitations of the instant claims and would therefore necessarily possess the ability to reduce the amount of active hsp27 as instantly claimed. As stated in the MPEP (see MPEP 2112), something that is old does not become patentable upon the discovery of a new property. Therefore, claims 14-17, 19 and 25-28 are anticipated by Baracchini et al.

Claims 14, 15, 25 and 26 are rejected under 35 U.S.C. 102(a) or (e) as being anticipated by Brophy et al. (U.S. 2003/0060399 A1).

The instant invention is drawn to a pharmaceutical composition comprising a therapeutic agent, more specifically an antisense oligonucleotide, effective to reduce the amount of active hsp27 and a pharmaceutically acceptable carrier, wherein the composition is packaged in an injectable dosage unit form.

Brophy et al. teach pharmaceutical compositions comprising a polypeptide and an inhibitor of HSP27. Brophy et al. teach that inhibitors of HSP27 include anti-sense HSP27 nucleic acids or small molecule inhibitors of the phosphorylation of HSP27 (see page 8). The pharmaceutical compositions thereof may be administered by any suitable route, including dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants, and vehicles (see page 8). Additionally, the composition can be injected or inhaled. Therefore, claims 14, 15, 25 and 26 are anticipated by Brophy et al.

Claims 14 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Hargis et al.

The instant invention is drawn to a pharmaceutical composition comprising a therapeutic agent, more specifically an antisense oligonucleotide, effective to reduce the amount of active hsp27 and a pharmaceutically acceptable carrier.

Hargis et al. teach antisense oligonucleotides that were used to lower levels of Hsp27 in medium. Buffers and water used by Hargis et al. are considered

pharmaceutically acceptable. Therefore, claims 14 and 15 are anticipated by Hargis et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 14-17, 19 and 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horman et al., in view of Taylor et al., Baracchini et al. (U.S. 5,801,154), and Bennett et al. (U.S. 5,998,148).

The invention of the above claims is drawn to pharmaceutical compositions comprising a therapeutic agent, more specifically a 12 to 35 nucleotide modified antisense oligonucleotide that reduces the amount of active hsp27 in cancerous cells and a pharmaceutically acceptable carrier. The composition is packaged in a dosage unit form, wherein the dosage unit form is an injectable solution. The invention is further drawn to antisense oligonucleotide comprising a consecutive series of bases as set forth in SEQ ID NO: 82.

Horman et al. teach anti-sense inhibition of HSP27 expression in MCF-7 mammary-carcinoma cells. MCF-7 cells were transfected with a modulatable human hsp27 anti-sense cDNA. The antisense cDNA utilized by Horman et al. would

inherently comprise a consecutive series of bases as set forth in SEQ ID NO: 82. Additionally, Horman et al. teach that HSP27 is over-expressed in pre-malignant and malignant lesions in rat and human liver (see paragraph 1).

Horman et al. do not teach modified antisense oligonucleotides 12 to 35 nucleotides in length, modified siRNA molecules 16 to 49 nucleotides, or injectable dosage unit solutions.

Taylor et al. teach that antisense oligonucleotides 7-30 nucleotides long can be synthesized to inhibit the expression of any protein provided the cDNA sequence is known. Taylor et al. also indicate that making and using such oligos are available to those of ordinary skill in the art, that it is common practice to chemically modify the such oligonucleotides to prolong their bioactivity, and also teach that with software analysis and high affinity oligos, one needs to screen only 3-6 oligos to find one that inhibits its target 66-95% (p. 565).

Baracchini et al. teach that antisense oligonucleotides can be used for research purposes, and also teach that preferred antisense oligonucleotides are modified in their sugar, backbone linkage and nucleobase composition (col. 6). Baracchini teaches that such modifications are desirable in antisense oligos because these modifications have desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid targets and increased stability in the presence of nucleases. Baracchini et al provide specific embodiments of such modifications at columns 6-8 and in Example 1. These specific examples taught by Baracchini et al include the presently claimed phosphorothioate linkages, 2'-O-methoxyethyl sugars, 5-methylcytosine and chimeric

oligonucleotides. Tables 1-4 show the successful design and use of modified oligonucleotides in cells in culture. Table 1 exemplifies the successful practice of general antisense design taught at columns 8-10. Column 4 teaches various carriers for antisense delivery. Baracchini et al. also teaches at column 8 that antisense oligonucleotides are preferably 8 to 30 nucleotides and that it is more preferable to make antisense oligonucleotides that are 12 to 25 nucleotides in length. Baracchini et al. teach dosing, as well as injection as a method of administration (see columns 4 and 5). Baracchini et al. teach targeting oligonucleotides specifically to the translation initiation site (see for example, claim 4). Baracchini et al. is considered to comprise a detailed blueprint for how to make and use inhibitory antisense oligos to target any known gene.

The teachings of Bennett et al. are considered to parallel those of Baracchini et al. Bennett et al. teaches general antisense targeting guidelines at columns 3-4. Bennett teaches, in column 5, for example, that antisense compounds are commonly used as research reagents and diagnostics. Column 5 indicates that antisense oligonucleotides 8-30 nucleotides in length are particularly preferred. Columns 10-24 teach numerous "carriers" for antisense oligonucleotides. Thus, Bennett et al. is also considered to comprise a detailed blueprint for how to make and use inhibitory antisense oligos to target any known gene.

It would have been obvious to one of ordinary skill in the art to use the cDNA sequence to inhibit HSP27 as taught by Horman et al. because Horman et al. teach that HSP27 is over-expressed in pre-malignant and malignant lesions. Therefore, it would

have been obvious to reduce the amount of active hsp27 in order to further study the role of hsp27 in cancer. Additionally, it would have been obvious to use antisense oligos as a tool to inhibit the expression of hsp27, as oligos 8-30, or 12-25 nucleobases in length were known to be advantageous at the time the invention was made, as demonstrated by Baracchini et al. and Bennett et al. Additionally, it would have been obvious to one of ordinary skill in the art to provide the oligonucleotide in a pharmaceutically acceptable composition, to modify the backbone of the oligonucleotide to increase resistance to nucleases, as well as to administer the composition via an injectable dosage format, as each of these are taught by Baracchini et al. It would have been obvious to target an oligonucleotide to the translation initiation site, as taught by Baracchini et al. As disclosed on page 5 of the instant specification, instantly claimed SEQ ID NO: 82 is an antisense oligonucleotide targeted to the translational initiation site of *hsp27* mRNA.

One would have been motivated to create such compounds because Horman et al. teach antisense inhibition of HSP27, as well as the overexpression of HSP27 in pre-malignant and malignant lesions. One would have been motivated to design an antisense oligonucleotide 8-30 or 12-25 nucleobases in length for this purpose, as taught by Taylor et al., Baracchini et al., and Bennett et al., as well as incorporate the antisense oligonucleotide into a pharmaceutical composition as taught by Baracchini et al. and Bennett et al., because each teach such compositions are beneficial for efficient delivery of the oligo. One would have been motivated to modify the backbone of the oligonucleotide for the benefits taught by Baracchini et al., such as enhanced cellular

uptake, enhanced affinity for nucleic acid targets and increased stability in the presence of nucleases. One would have been motivated to target the translation initiation site, as this was a routine target site at the time the invention was made, as demonstrated by Baracchini et al. Finally, one would have been motivated to deliver the composition with an injectable dosage unit form, because injection and dosage units were both routine for administration in the art at the time the invention was made, as demonstrated by Baracchini et al.

One would have a reasonable expectation of success given that Taylor teaches that with software analysis and high affinity oligos, one needs to screen only 3-6 oligos to find one that inhibits its target 66-95%, and since Baracchini et al. and Bennett et al. both teach making modified antisense compounds targeted to distinct regions of a target gene, including the translation initiation site, the steps of which are routine to one of ordinary skill in the art.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is 571-272-0755. The examiner can normally be reached on Mon-Fri 7:00 am – 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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Amy H. Bowman
Examiner
Art Unit 1635

JAMES SCHULTZ
PATENT EXAMINER